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Mini Review

The Molecular Mechanisms of CD19-Negative Relapse in B-Cell Lymphoma after CAR T-Cell Immunotherapy

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Abstract

The chimeric antigen receptor T cell (CAR T-cell) immunotherapy is the most antitumor ability in relapse/refractory (R/R) hematological malignancies but it still shows a high relapse rate. A few studies have been found that the molecular mechanisms of CD19-negative relapse after CAR T-cell therapy are the CD19 loss or down-regulation in lymphoma, including lineage switching, CD19 gene mutation, selective shearing, and subcloning of CD19-negative cell. The gene rearrangement, fusion genes and IL-6 may be to influent the therapeutic effect of CAR T-cell immunotherapy. The gene mutations of APX5, IKAROS, EBF1, GNA13, SOCS1, TNFALP3, XPO1, FLT3 etc. have been currently found after CAR T-cell therapy relapse. The review reports the molecular mechanisms of CD19-negative relapse in B-cell lymphoma after CAR T-cell immunotherapy.

Keywords: CD19-negative relapse, B-cell lymphoma, CAR T-cell immunotherapy, Molecular mechanisms

Introduction

CAR T-cell immunotherapy is a great advance in the treatment of hematologic malignancies. Some researches find that the complete remission rate about 70%-90% for relapsed/refractory B-cell acute lymphocytic leukemia [1]. However, a study has also found that relapse rate of lymphoma is about 30-50% after CAR T-cell treatment. We have reported that there are two main causes for CD19-positive and CD19-negative relapse after CAR T-cell immunotherapy [2-4]. CD19-positive relapse is mainly due to low efficiency and persistence, senescence of CAR T-cell *in vivo*. And there are also some confounding factors such as: different co-stimulatory, the manufacture methods, various categories and dosage of CAR T-cell, tumor heterogeneity and so on [2,3]. The main mechanisms of CD19-negative relapse after CAR T-cell therapy may be the presence of the loss or down-regulation of CD19 expression. The effects of other molecular, still unclear genetic mutations, and the indirect effects of other cytokines may influent the expression of CD19.

Directly Related Molecular Mechanisms

The CD19 loss may be due to lineage switch mutation of CD19 gene or selective shearing and subcloning of CD19-negative cells.

Lineage Switch

The lineage switch is the interconversion of the B-lymphocyte lineage with the myeloid cell lineage. MLL-B-cell acute lymphoblastic leukemia /B-cell precursor ALL is malleable and reversible in mixed leukemia [5], which may occur myeloid transformation under the selective pressure in CAR T-cell immunotherapy. In recurrent cases, deletion or down-regulation of PAX5, IKAROS and EBF1 was found [6,7]. PAX5, located on chromosome 9, is a member of the coding paired-frame (PAX) family of transcription factors. It encodes 50-kD B-cell specific activator protein (BSAP), which is expressed in pre-B and mature B cells [8]. IKAROS, located at chromosome 7, encodes product is a zinc finger structure-containing transcription factor that plays a critical regulatory role in early lymphocyte

differentiation [9,10]. EBF1, located on chromosome 5, encodes platelet-derived growth factor receptor beta, a receptor tyrosine kinase consisting of 1106 amino acids [11]. PAX5, IKAROS and EBF1 are the main regulators of B cells. PU1 and C/EBP-α's are involved in myeloid expression. The Loss or downregulation of PAX5, IKAROS and EBF1 leads to failure of CD19 expression and continues expression of myeloid cell, which are causing the lineage switch [6,7].

Mutation or Selective Shearing of the CD19 Gene

The CD19 gene locates on chromosome 16. It has been shown that the DNA region expressing CD19 has mutations on exons 2-5, of which 4/5 are mutations on exon 3 [12]. Among the mutations, the most notable is on exon 2. SRSF3 splicing factor is also involved in CD19 expression. SRSF3, located on chromosome 6, encodes a protein that is a member of the serotonin/arginine (SR)-rich pre-mRNA splicing factor family [13]. The SRSF3 splicing factor is mainly involved in the retention of exon 2. Hence, the down-regulation of SRSF3 splicing factor also leads to the loss or down-regulation of CD19 [1, 4].

CD19-Negative Lymphocyte Subcloning

The clusters of CD19-negetive lymphoma were found in the patients who were before and after the CAR T-cell treatment. The same clusters of cells were found prior to CAR T-cell treatment, which indicated that patients had CD19 negative B-cells present and cloned before CAR T-cell treatment. In addition, the CD19 was monitored in patients of CD19-negative relapse with retained intron 2 showing non-functional CD19 expression. It may be a mechanism that leads to CD19-negative relapse in lymphoma [1].

Possibly Relevant Molecular Mechanisms

Mutations in ctDNA

The patients of relapse lymphoma have been found some mutated genes after CAR T-cell treatment. In one study, continuous monitoring results of circulating tumor DNA (ctDNA) in the patients revealed mutations of GNA13, SOCS1, XPO1T and TNFALP3 in ctDNA. GNA13, located on chromosome 17, corresponds to a monitoring region of exon1-4. It encodes the Gα13 protein, which acts to regulate cell morphology, contraction, migration and differentiation and maturation [14]. SOCS1, located on chromosome 17, corresponds to a monitoring region of CDS. It is an important member of the suppressor of cytokine signaling (SOCS) protein family. SOCS1 is involved in a variety of acute and chronic inflammatory responses, innate and acquired immune responses, hormone regulation, and the generation and development of many tumors in the body [15]. XPO1, located on chromosome 2, corresponds to a monitoring region of exon15-17 It is an important member of the importinβ family of nuclear export protein receptors, mainly responsible for the nuclear export of some tumor suppressor proteins and growth regulator proteins [16]. TNFALP3 corresponds to a monitoring region of CDS. There are few relevant studies about TNFALP3. The mutations of GNA13, SOCS1, XPO1T and TNFALP3 in ctDNA would exist associated with prognosis after CAR T-cell treatment [17].

Gene Rearrangement and Fusion Genes

Rearrangement of 11q23 occurs to patients with MLL-r, The most common of which is MLL-AF4. At present, fusion gene of ZNF384 in 12q13, as well as internal repeat crosstalk of the FLT3 gene, are also found in patients of relapse with lineage switch. FLT3, located on chromosome 13, encodes a class III receptor tyrosine kinase that regulates hematopoiesis. Activated receptor kinase phosphorylation activates multiple signaling pathways, including apoptosis, proliferation and differentiation of myeloid hematopoietic cells [18]. The gene rearrangement or fusion genes cause relapse of MLL remains to be investigated after CAR T-cell immunotherapy [5,19,20].

Indirectly Related Molecular Mechanisms

The IL-6 gene, encoded a cytokine that functions as inflammation and B-cell maturation, is located on chromosome 7. In a study, MLL patients with t (4,11) rearrangements who were treated with CAR T-cells developed cytokine release syndrome (CRS) [21]. The patients that occurred CRS developed myeloid relapse while the other patients that were in remission didn't occur CRS. It has also been shown that IL-6 can drive myeloid differentiation of lymphocytes or cloning of myeloid cells. The results show that IL-6 contributes to myeloid transformation in mixed leukemias [6].

Conclusion

The current research on CD19-negative relapse is thought to be the loss of CD19 after CAR T-cell immunotherapy. The lineage switching, CD19 gene mutation, selective shearing, and subcloning of CD19- negative are thought to result in the loss of CD19. Moreover, the IL-6, mutated and fused genes have also been discovered. Further studies are needed for its relapse mechanism.

Future Perspectives

CD19 is the most common target in CAR T-cell immunotherapy. CD22 is a target for salvage therapy after Anti-CD 19 CAR T-cell treatment [22]. The bispecific anti-CD20 and anti-CD19 CAR T-cells are also available to treat lymphoma [23]. The loss of surface antigens may lead to relapse. Therefore, research in the molecular field may be the way forward for CAR T-cell immunotherapy.

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